Endometrial carcinoma: treatment

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Conflict of interest
None.

Description of the evidence collection method
The bibliographic review of scientific articles was performed in the databases EMBASE, SciELO/LILACS, PubMed/Medline, and the Cochrane Library using the keywords (MeSH terms) grouped as follows: (endometrial neoplasm OR carcinoma, endometrial OR endometrial cancers OR endometrium cancer OR uterine neoplasm OR neoplasm, uterus OR uterus cancers OR cancer of the uterus OR uterine cancers) AND adenocarcinoma AND risk factors AND (neoplasm staging OR tumor staging OR cancer staging) AND neoplasm invasiveness AND neoplasm metastasis AND lymphatic metastasis AND (antineoplastic agent, hormonal OR hormonal antineoplastic drugs) AND medroxyprogesterone AND tamoxifen AND (neoplasm recurrence, local OR local neoplasm recurrence) AND recurrence AND (lymph node excision OR lymph node dissections OR node dissection, lymph) AND (adjuvant chemotherapy OR chemotherapy, adjuvant) AND (antineoplastic combined chemotherapy protocols OR antineoplastic agents, combined OR cancer chemotherapy protocol) AND (adjuvant radiotherapy OR radiotherapy, adjuvant) AND radiotherapy, high-energy AND combined modality therapy AND (laparoscopy OR surgical procedures, laparoscopic OR laparoscopic surgery OR laparoscopic surgical procedures) AND laparotomy AND postoperative complications AND follow-up studies.

Degree of recommendation and strength of evidence:

A: Experimental or observational studies of higher consistency.

B: Experimental or observational studies of lesser consistency.

C: Case reports (non-controlled studies).

D: Opinion without critical evaluation, based on consensuses, physiological studies or animal models.

Objective

To evaluate the main approaches in the treatment of endometrial carcinoma according to the available evidence.

Introduction

Endometrial cancer is one of the most common malignant neoplasms of the female genital tract in Western Europe and North America[1,2] (**D**).

More than 90% of cases occur in women older than 50 years (mean age 63 years), contributing to 1% to 2% of all causes of death by cancer. The most common symptom is vaginal bleeding and when diagnosed soon after symptoms onset, the disease is limited to the uterus in more than 75% of patients, therefore in its early stages, with favorable prognosis and high rates of overall survival (80% to 85%) in five years[3] (**D**).

The International Federation of Gynecology and Obstetrics (FIGO) introduced in 1988 and updated in 2009 the staging system for endometrial cancer, which is surgical-pathological and defined after total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and periaortic lymphadenectomy, and peritoneal cytology; the prognosis depends on age, histology and tumor grade, depth of invasion in the myometrium, cervical involvement, and lymph node metastasis[4,5](**B**)[6](**C**)[7](**D**).

1. Does the use of adjuvant endocrine therapy in patients with endometrial carcinoma result in overall survival improvement?

The primary treatment of endometrial carcinoma, mainly represented by surgery and radiotherapy, especially in cases of undifferentiated tumors with deep myometrial infiltration, does not show favorable results in tumor control. As endometrial carcinoma is a hormone-dependent disease, the hypothesis that the use of adjuvant endocrine therapy might result in improvement has been supported, preventing recurrence and death in patients with the disease at early stages[8-11](**A**).

In a prospective study, evaluating women with a mean age of 63 years submitted to surgical therapy (abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial colpectomy) with histological diagnosis of endometrial carcinoma stage I or II (FIGO), of which 57% were

stage IB and subsequently submitted to adjuvant endocrine therapy with the use of medroxyprogesterone acetate (MPA) at a dose of 500 mg/day or tamoxifen 30 mg/day for a mean period of 56 months, overall survival was similar in both treatment groups when compared with control group, ARR = 0.001 with 95% CI (-0.090-0.092) and ARR = -0.023 with 95% CI (-0.001-0.163) for the MPA and tamoxifen, respectively[12](**B**).

Regarding the adverse effects, they occurred more frequently in users of MPA and tamoxifen (59% and 49% respectively), with deterioration of glycemic control and peripheral edema more often observed with the use of MPA[12] (**B**).

Recommendation

In patients with early-stage endometrial carcinoma, there is no indication for the use of adjuvant endocrine therapy.

2. Is the performance of a pelvic lymphadenectomy in patients with early-stage endometrial carcinoma related to better results regarding overall survival and recurrence?

Endometrial carcinoma most frequently develops in the posterior wall and fundus of the uterus, spreads continuously through the uterine body by myometrial invasion and cervical involvement, and has as its most frequent site of metastasis the retroperitoneal lymph nodes (pelvic lymph nodes), and less frequently, the periaortic lymph nodes. Patients with early-stage endometrial carcinoma (stage I) have metastasis in the pelvic lymph nodes at a frequency of approximately 10%.

Considering the same staging technique, patients with superficial myometrial invasion by well-differentiated tumor present lymph node involvement in about 3% to 5% of cases, and this proportion increases to 20% in poorly differentiated tumors and deep myometrial invasion. It is also known that in cases of retroperitoneal lymph node involvement of both pelvic and periaortic lymph nodes, the prognosis for five-year survival is compromised, with variable rates of 44% to 52%[13](**D**). Thus, tumor grade, depth of invasion, and tumor type were prognostic factors of paramount importance, used to predict the possibility of recurrence as well as the need for the use of adjuvant therapy.

Since 1988, when FIGO introduced the need for lymphadenectomy for the staging of endometrial cancer, many questions have been raised, mainly regarding the extent of lymphadenectomy, indications, risks, and benefits related to overall survival and recurrence.

Although some retrospective studies have shown an association between lymphadenectomy and improvement in survival rates, others with high strength of evidence are not in agreement with these results[14,15](**B**).

A multicenter randomized trial that evaluated patients with a mean age of 62 years and histological diagnosis of endometrial carcinoma limited to the uterine corpus (FIGO stage I) submitted to standard surgical procedure (total abdominal hysterectomy with bilateral salpingo-oophorectomy) associated or not with systematic pelvic lymphadenectomy and mean follow-up of 49 months showed no influence of the performance of the lymphadenectomy in both the number of recurrences (12.9% versus 13.2% respectively), and overall survival. There was also a larger number of metastases in lymph nodes and staging changes (13.3% versus 3.2% of stage IIIC) with or without the performance of the lymphadenectomy, respectively[16](**A**).

Similar results were found in another randomized study, where during the mean follow-up of 37 months, women with early-stage endometrial carcinoma submitted primarily to standard surgical therapy (total abdominal hysterectomy with bilateral salpingo-oophorectomy) with or without lymphadenectomy, showed no clear benefits in terms of survival[17](**A**).

Recommendation

In patients diagnosed with early-stage endometrial carcinoma, the performance of pelvic lymphadenectomy associated with standard surgery (total hysterectomy and bilateral salpingo-oophorectomy), allows for the attainment of a more appropriate staging, by increasing the detection of lymph node metastases. It does not show, however, improvement in overall survival or reduction in the recurrence rate.

3. Does the indication for adjuvant pelvic radiotherapy in surgically-treated patients with early-stage endometrial carcinoma determine improvement in the control of locoregional recurrences?

As mentioned before, the most significant prognostic factors in endometrial carcinoma are the stage, histological grade, and depth of myometrial invasion. Other factors are the patient's age, tumor histological type, peritoneal cytology, progesterone receptor activity, and uterine size[18,19](**B**). In the presence of high-risk factors for recurrence, such as myometrial invasion ≥ 50% or histological grades 2 or 3, pelvic radiotherapy is indicated. In a retrospective analysis, patients with stage I endometrial carcinoma treated surgically and submitted to adjuvant radiotherapy showed overall survival rates in five years ranging from 80% to 95%, and locoregional recurrence rates of approximately 4% to 8% [20](**A**)[21](**B**).

In a prospective, randomized study evaluating women with a mean age of 66 years, with stage I endometrial carcinoma, histological grade 1, and myometrial invasion ≥ 50%;

or histological grade 2 with any degree of invasion; or histologic grade 3 with invasion < 50%; submitted or not to adjuvant pelvic radiotherapy totaling 46 Gy total dose, it was observed during a mean follow-up of 52 months, that locoregional recurrences are more often diagnosed in patients not treated with radiotherapy (14% versus 4% respectively with ARR = 0.080 and 95% CI: 0.043-0.117), with most recurrences limited to the vagina. Regarding overall survival, no significant difference is observed between patients undergoing radiotherapy or not (ARR = -0.028 95%CI: 0.080-0.024). Regarding adverse events, it was observed that late complications are more frequent in patients undergoing adjuvant radiotherapy (25% versus 6% respectively, with $p < 0.001$), representing 1/3 of the severe complications[22](**A**).

When expanding the assessment to a period of 97 months, a continued reduction in locoregional recurrence in patients undergoing adjuvant radiotherapy was observed (5% versus 14% respectively, with $p < 0.0001$)[23](**B**).

Recommendation

The use of adjuvant radiotherapy in patients with early-stage endometrial carcinoma showed a reduction in locoregional recurrences but no influence on survival. Due to the adverse events related to the use of adjuvant radiotherapy, this should not be the treatment of choice to prevent local recurrence only, and therefore, it is not recommended for early-stage carcinomas in the absence of risk factors for metastases.

4. Is laparoscopic surgery safe and effective in the treatment of endometrial carcinoma?

The standard approach for the treatment and staging of endometrial carcinoma consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, periaortic and pelvic lymphadenectomy, and peritoneal lavage[4](**D**). However, in recent years, there has been a growing interest in surgical techniques for the treatment of gynecological malignancies, particularly laparoscopic surgery, in the treatment of endometrial carcinoma[24](**B**)[25](**C**). Compared with laparotomy, the laparoscopic surgery has advantages such as smaller incisions, better visibility of the surgical field, less blood loss, less postoperative pain, faster postoperative recovery with shorter hospitalization, and faster return to usual activities, with no surgical limitations for obese and older patients[26-29](**B**).

Regarding the overall survival and number of recurrences, prospective and retrospective studies have shown no significant difference between the laparoscopic and laparotomy techniques for the treatment of patients with early-stage endometrial carcinoma[30,31](**B**). The same can be observed with respect to intraoperative complications[32](**B**).

In a prospective randomized study that assessed women with early-stage endometrial carcinoma (stage I) submitted to laparotomy or laparoscopy, and a mean follow-up of 38 months, no significant differences were observed in both the number of recurrences between the two approaches (11.5% versus 8.6% respectively) and intraoperative complications[33](**A**). Another prospective study of patients with early-stage endometrial carcinoma treated by laparoscopy or laparotomy had a longer follow-up of seven years, aiming at evaluating recurrences and no significant difference was observed between the two procedures (20% versus 18.4% respectively, with $p = 0.860$)[34](**A**).

Recommendation

Although the laparoscopic approach is not the standard treatment for endometrial carcinoma, when performed by trained professionals it has shown to be a safe and effective alternative for the treatment of early-stage endometrial carcinoma without compromising the required oncological stringency.

5. Does the use of adjuvant chemotherapy in patients with high-risk endometrial carcinoma (stages Ib G3, II G3 with myometrial invasion > 50%, and stage III) demonstrate benefits in terms of overall survival when compared to pelvic radiotherapy?

Approximately 10% to 15% of patients with early-stage endometrial carcinoma will have disease recurrence[22](**A**)[35](**B**). Thus, both chemotherapy and radiation therapy have been used aiming at the reduction in recurrence rate. However, the best therapeutic approach remains controversial. Randomized trials assessing adjuvant radiotherapy for early-stage endometrial carcinoma have shown a significant reduction in locoregional recurrences, but no influence on survival[22](**A**). As a result, studies using chemotherapy and/or radiotherapy as adjuvant treatments have been developed in an attempt to improve survival.

In a multicenter randomized study, patients with a mean age of 59 years who had endometrial carcinoma stages IC (61%) to IIIC (11.9%) with myometrial invasion > 50%, originally submitted to total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and periaortic lymphadenectomy (performed in 96% and 28% of patients, respectively) were evaluated. After the surgical procedure, pelvic radiotherapy at a dose of 45-50 Gy and a CAP chemotherapy regimen (cyclophosphamide, doxorubicin, and cisplatin) was used. There was no significant difference in both the number of recurrences (both intra and extra-pelvic) between the two approaches (ARR = -0.006 95% CI: -0.057-0.045, and ARR = -0.026 95% CI: -0.097-0.045 respectively) and overall survival (ARR = -0.036 95% CI: -0.108-0.036) after 59 months of follow-up[36](**A**). Another randomized study,

using the same chemotherapy and radiotherapy regimen in patients with high-risk endometrial carcinoma, also failed to demonstrate, during the evaluation period of 95 months, any difference between treatments regarding the increase in disease-free survival and overall survival (ARR = 0.039 95% CI: -0.062-0.140, and ARR = -0.003 95% CI: -0.052-0.046, respectively)[37](**B**).

Recommendation

Both chemotherapy and adjuvant pelvic radiotherapy in patients with high-risk endometrial carcinoma demonstrate no significant difference regarding overall survival.

6. Does the use of chemotherapy associated with radiotherapy indicated in the treatment of high-risk endometrial carcinoma show better results in terms of distant metastases when compared to radiotherapy alone?

The myometrial invasion, histological tumor grade, and presence of extrauterine disease are associated with high incidence of cervical and adnexal involvement and metastasis to retroperitoneal lymph nodes[4,38](**B**)[39](**C**). Adjuvant radiotherapy used in high-risk endometrial carcinoma (myometrial and cervical invasion and advanced histological grade) has shown consistent results in reduction of locoregional recurrence but without modifying distant involvement, a factor that interferes with survival rates[22](**A**). Thus, the combination of radiation therapy and chemotherapy began to be evaluated in order to increase overall survival.

When evaluating patients with a mean age of 74 years, with stages IA-B endometrial carcinoma and histological grade 3 or stages IC-IIIA with histological grades 1-3, originally submitted to total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy performed in 80% of the patients, and after pelvic radiotherapy (total dose of 56 Gy) or pelvic radiotherapy associated with chemotherapy consisting of three cycles of 50 mg/m^2 cisplatin, 60 mg/m^2 of epirubicin, and 500 mg/m^2 of cyclophosphamide; after a follow-up of five years, it was observed that the combined regimen was not able to prevent the occurrence of distant metastases (liver, retroperitoneal lymph nodes, lungs, bones, and brain), with rates of 20.2% versus 13.9% for the chemotherapy associated with radiation therapy and radiotherapy alone, respectively, the difference was not significant (ARR= -0.063 with 95% CI: -0.180-0.054)[40](**A**). There was no significant difference in survival of patients when comparing the two regimens (82.1% versus 84.7% for chemotherapy associated with radiotherapy and radiotherapy alone, respectively, with ARR= -0.026 and 95% CI: -0.143-0.091)[40](**A**).

Recommendation

The use of chemotherapy associated with radiotherapy in patients with high-grade endometrial carcinoma shows no reduction in rates of distant metastases and does not improve overall survival.

7. Is the use of chemotherapy in patients with advanced endometrial carcinoma (stages III or IV) associated with higher overall survival, when compared to radiotherapy alone?

Patients with advanced-stage endometrial carcinoma are rarely candidates for surgery. Stages III and IV endometrial carcinoma presents as a heterogeneous group of tumors with varied prognosis, and individualization of treatment should be performed according to the disease extension[41](**B**). Considering the high recurrence rates, in recent years total abdominal radiotherapy has been used;, for the treatment of extra-abdominal metastases, chemotherapy is indicated, with substantial improvements in overall survival rates of these patients but without neglecting the cytotoxicity of chemotherapy[42,43](**A**)[44-46](**B**).

In patients with stages III or IV endometrial carcinoma, initially subjected to cytoreductive surgery, with residual disease < 2.0 cm, and subsequently treated with total abdominal radiotherapy and pelvic reinforcement (30 Gy + reinforcement of 15 Gy) or with chemotherapy consisting of eight cycles of 60 mg/m^2 of doxorubicin combined with 50 mg/m^2 of cisplatin, and a follow-up period of 74 months, there was significant increase in overall survival with the chemotherapy regimen (51% versus 38% for chemotherapy and radiotherapy, respectively, with ARR= -0.129 and 95%CI: -0.226 to -0.032)[47](**A**).

Regarding adverse events, it is noteworthy that they, particularly hematological grades 3 and 4, gastrointestinal, cardiac, and neurological, are significantly more frequent with the use of chemotherapy[47](**A**).

Recommendation

Patients with advanced-stage endometrial carcinoma (stages III or IV) show significant improvement in overall survival with the use of chemotherapy, but it is associated with a higher frequency of adverse events.

8. What is the best follow-up strategy in patients treated for endometrial carcinoma who are clinically disease-free?

The concept of long-term surveillance of patients treated for endometrial carcinoma with curative intent is based on the premise that early detection results in decreased morbimortality associated with recurrence. Currently, follow-up protocols are highly variable, using different diagnostic tests and various intervals. Thus, there is no formal recommendation regarding the monitoring and follow-up of these patients[48](**D**).

The main factors associated with survival time and recurrence of disease are represented by tumor grade and histology, depth of myometrial invasion, metastasis to lymph nodes, and presence of extrauterine disease[49](**B**). The anatomical locations of recurrences are roughly equivalent both locally (pelvic) and at distance (abdomen and thorax); the most common sites of involvement are the vaginal cuff, pelvis, and lungs[50](**A**)[51](**B**). Regarding rescue rates by appropriate therapy in cases of recurrence, there are controversies, and some publications have shown values that vary from 10% to 38% [52](**C**)[48](**D**).

When evaluating retrospective studies reporting strategies for the follow-up of patients receiving potentially curative treatment for endometrial carcinoma and who were clinically free of disease at the beginning of the evaluation, it was observed that most recurrences (recurrence rate of 13% among the studies) occurred on average in the first three years after treatment completion (ranging from 2 to 3.5 years of follow-up) and of these, 77% were symptomatic[53](**A**)[54-58](**B**).

Regarding follow-up intervals, it was observed that these were variable between studies (ranging from 12 to 32 consultations during a five-year follow-up period), and the tests performed to detect recurrences consisted mainly of physical examination, vaginal cytology, and chest radiography. The use of ultrasound, computed tomography (CT), and CA 125 measurement were not used, in general, as part of the routine follow-up studies[54,56,59](**B**).

The detection of asymptomatic recurrence in the studies ranged from 5% to 33% for patients undergoing physical examination, 0% to 4% with vaginal cytology, 0% to 14% with chest X-ray, 4% to 13% with abdominal ultrasonography, 5% to 21% with abdominal/pelvic CT, and 15% in patients selected for CA 125 measurement, and there is no clear evidence that the request for such examination reduces mortality in recurrent disease[60](**A**).

The request for mammography and Pap smear collection should follow the guidelines of breast and cervical cancer screening. For patients at risk for colon cancer, a colonoscopy must be requested and the need for endoscopy should be evaluated.

Recommendation

There is no evidence that follow-up examinations in asymptomatic women with normal test results reduce mortality. Periodic consultations up to a period of three years of follow-up (every three or four months) are recommended, with anamnesis aimed at test requests according to symptoms and abnormal test results. After this, the consultation period may be twice a year for five years, and then annually[60](**A**).

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